ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

Thyroid Dysfunctions in Patients with Hepatocellular Carcinoma Treated by Transarterial Chemoembolization

Amal Tohamy Abdelmoez[1]*, Ahmed Abbas Elkhattib[1], Amany M Maher[2] and Ahmed Kamal ElDorry[3]

[1]*Tropical Medicine Department, Ain Shams University, Egypt*

[2]*Medical Research Center, Molecular Biology Unit, Ain Shams University, Egypt*

[3]*Radiology Medicine, Egypt*

***Corresponding Author**: Amal Tohamy Abdelmoez, Assistant Professor of Tropical Medicine, Ain Shams University, Egypt.

Received: October 17, 2019; **Published:** February 08, 2020

Abstract

Background: Trans-arterial chemoembolization (TACE) involves the application of iodide in the form of lipiodol mixed with a chemotherapeutic agent Although required for thyroid hormone synthesis, excess intra-thyroid iodide can paradoxically decrease hormone synthesis.

Aim: Evaluation of the thyroid dysfunctions after TACE for patients with hepatocellular carcinoma.

Patients and Methods: We included 30 patients with hepatocellular carcinoma who were eligible for TACE. We excluded patients with history of antiviral therapy, thyroid diseases and residence in iodine deficiency areas. After written consent, all patients were subjected to history taking, clinical examinations and laboratory investigations (liver profile, renal functions tests) and TSH, FT3, FT4 before TACE, one weak and one month later.

Results: After one week TSH, FT3, and FT4 levels were high in 4 patients (13.3%), 2 patients (6.7%), 5 patients (16.7%), and low in one patient (3.3%), 2 patients (6.7%),3 patients (10%) and normal in 25 patients (83.3%), 26 patients (86.7%), 22 patients (73.3%) respectively with significant difference ($p < 0.05$). One month later the levels were high in (0%),4 patients (13.3%),9 patients (30%) low in 3 patients (10%), one patients(3.3%), no patients (0%) and normal in 27 patients (90%), 25 patients (83.3%), 21 patients (70%) respectively with a significant difference (< 0.05).

Conclusions: Thyroid dysfunctions after TACE presented in 16.7% of patients and could be hypo or hyper-thyroidism.

Impact: This work results are important as TACE is an important technique for treatment of hepatocellular carcinoma and can be used several times and so the risk for thyroid disorders is increased. These results recommend that patients with hepatocellular carcinoma must have their thyroid functions checked before and after TACE.

Keywords: *TACE; Thyroid; Iodine*

Introduction

Transarterial chemoembolization (TACE) was introduced as a palliative treatment in patients with unresectable HCC, it has become one of the most common forms of interventional therapy [1].

Nowadays TACE is often performed by selective catheterization of the hepatic segmental arteries nourishing the HCC lesions, to limit as much as possible the injury to the surrounding non tumorous liver. The procedure involves the application of iodide in the form of iodized oil as a radiopaque contrast medium, for example lipiodol mixed with a chemotherapeutic agent [2].

Lipiodol and related compounds are products of the addition (not substitution) of iodine to double bonds of the unsaturated fatty acids of certain plant oils (poppy seed oil) most of which have a very high percentage of unsaturated fatty acids [3].

ICM, (lipiodol), represents a significant iodine load: a single dose contains 13,500 μg of free iodide, as well as 15-60 g of bound iodine that may be liberated to free iodide following administration [4,5]. The implied iodide load is 90-to-several-hundred-thousand-fold the daily recommended intake for adults (150 mcg) [6,7]. This study aim of the work was evaluation of the thyroid dysfunctions in hepatocellular carcinoma patients treated with TACE.

Patients and Methods

This work is cross sectional study conducted in hepatocellular carcinoma HCC clinic Tropical Medicine department Ain Shams University hospitals from June 2014 to December 2014.We obtained approval of the local ethical committee of the department which is in accordance with Helsinki declaration 1975. The study included 30 patients with proved diagnosis of HCC according to Barcelona clinic liver cancer (BCLC) 2010 after written consent were subjected to TACE [8]**.** We excluded patients with history of any thyroid disorders, administration of antiviral treatment or residents in Iodine deficiency areas.

Methods

All the patients were subjected to the following before the TACE procedure: full history taking and clinical examination, with special stress on thyroid disorders manifestations, laboratory investigations (complete blood count, ALT, AST, creatinine, serum alphafetoprotein), and thyroid hormones (TSH, free T3, free T4).

After TACE procedure

Patients were re-subjected to thyroid profile (free T3, free T4, and TSH) after one week and one month later. Also history taken and clinical examination for symptoms and signs suggesting thyroid dysfunction after TACE were done.

KIT

B7K Architect free T3, free T4, TSH reagent kits, U.S.A

Principle of the assay

The architect free T3, T4, TSH assay is a chemi-luminescent micro-particle immunoassay (CMIA) for the quantitative determination of free T3, T4, TSH in human serum, plasma.

Sample

Serum

Blood should be drawn using standard vein-puncture techniques, collected in serum separator tubes), or plasma collected in EDTA anti- coagulant tubes.

For optimal result the specimens should be free of bubbles, fibrin, red blood cells, other particulate matters. Ensure that complete clot formation in serum specimens has taken place prior to centrifugation, if testing will be delayed more than 24 hours, remove serum or plasma from the clot, serum separator or red blood cells, specimens may be stored for up to 6 days at 2-8 0c prior to being tested.

If test will be delayed more than 6 days, specimens should be frozen at -10 0c or colder and will show no performance difference.

Calibration and results

For free T3

Calibrator range 0.0-30.0pg\ml.

The architect free t3 assay utilizes a 4 parameter logestic curves fit data reduction method (4plc, y weighted) to generate a calibration curve.

The default result unit for the architect free T3 is pg/ml. when the alternate result unit, P.mol/L is selected the conversion formula is (Concentration in pg/ml)*(1.536) =concentration in p.mol/L.

Expected values

Normal range of 1.71 pg/ml to 3.71 pg/ml.

For free T4

Calibrator range: 0.0-6.0 ng/dl.

The architect free T4 assay utilizes a 4 parameter logestic curves fit data reduction method (4plc, y weighted) to generate a calibration curve.

The default result unit for the architect free T4 is ng/dl. when the alternate result unit, pmol/L is selected the conversion formula is (Concentration in ng/dl)*(12.87)=concentration in pmol/l.

Expected values

Normal range of 0.70 ng/dl to 1.48 ng/dl.

For TSH

Calibrator range: 0.0000 to 100.0000 µiu/ml.

The architect free TSH assay utilizes a 4 parameter logestic curves fit data reduction method (4plc,y weighted) to generate a calibration curve.

The default result unit for the architect free T4 is µiu/ml. when the alternate result unit miu/mL is selected the conversion formula is (Concentration in µiu/ml)*(1) = concentration in miu/ml.

Expected values

Normal range of .35 µiu/ml to 4.94 µiu/ml.

TACE procedure: using percutaneous endovascular techniques, transarterial chemoembolization (TACE) was performed by selective catheterization of the hepatic segmental arteries nourishing the lesions, using either 5-F catheters (Simmons 1 and Cobra; Mallinckrodt, St Louis, USA or Hydrophilic Simmons 1 and Cobra; Terumo, Tokyo, Japan) or 3-F coaxial microcatheters (Tracker 18; Vascular Access System, Target, St José, USA; SP Catheter; Terumo). TACE was used to deliver potent anticancer drug directly into tumor-feeding arteries. As a result, tumors were exposed to very high drug concentrations, while systemic exposure was minimized. The cytotoxic lipiodol mix-

ture was prepared by mixing 100 mg adriablastin powder with 10 cc of saline, water soluble contrast and 10 cc of oily contrast (lipiodol ultra-fluid) to ensure a homogenous mixture, the embolization was done using gel foam particles cut into small pledges and mixed with water soluble contrast.

Statistical analysis was applied on the obtained data, using the following methods:

IBM SPSS statistics (V. 22.0, IBM Corp., USA, 2013) was used for data analysis. Data were expressed as Mean ± SD for quantitative parametric measures in addition to Median Percentiles for quantitative non-parametric measures and both number and percentage for categorized data. Ranked Sperman correlation and Chi-square tests were used. The probability of error at 0.05 was considered Significant, while at 0.01 and 0.001 are highly significant.

Results

Descriptive data of the studied patients are shown in table 1. There were sub-clinical changes in the thyroid hormones levels in some patients after exposure to TACE, showing increasing or decreasing in their level. Concerning changes in TSH level we found that after one weak we had 4 patients (13.3%) with high levels, one patient (3.3%) with low level, and 25 patient (83.3%) stay within normal. One month later the 4 patients (13.3%) with high TSH level got their level normal, and one patient with low TSH level still had it low. Also 2 (8%) patients with normal TSH level at one week got low TSH level at one month after TACE with statistically significant difference ($p < 0.05$) table 2. Also changes in FT4 level were as follows after one weak 5 patients (16.7%) had high level, and 3 patients (10%) had low level, one month later 9 (30%) patients had their FT4 level high, and all 3patients with low level become normalized with statistically significant difference ($p < 0.05$) table 3. Moreover changes in FT3 showed that changes in FT3 after one weak there were 2 patients (6.7%) had high FT3 level and 2 patients (6.7%) had low FT3 level, after one month there were 4 patients (13.3%) had high FT3level and one patient (3,3%) had low FT3 level with no statistically significant difference ($p > 0.05$) table 4. Also there were statistically non-significant correlation between these changes in thyroid hormones and age, sex, residence, laboratory investigations ($p > 0.05$).

Discussion and Conclusion

Excess intrathyroid iodide can paradoxically decrease the organification of iodide and subsequent hormone synthesis, a phenomenon first described in vivo in the rat by Wolff and Chaikoff in 1948 and termed the “acute Wolff-Chaikoff effect” [9,10]. The iodide-induced

Variables		Mean ± SD	Range
Age (years)		54.9 ± 5.17	(43-64)
Variables		Number	Percent %
Sex	Male	24	80%
	Female	6	20%
Smoking	Smoking	7	23%
	Non-smoking	23	77%
Residence	Urban	6	20%
	Rural	24	80%
DM	Diabetic	12	40%
	Non diabetic	18	60%
Child class	A	18	60%
	B	12	40%

Table 1: *Demographic data of the studied group.*

			1m	1w	Bef.	Total
TSH	High	Count	0	4	0	4
		%	0.0%	13.3%	0.0%	4.4%
	Low	Count	3	1	0	4
		%	10.0%	3.3%	0.0%	4.4%
	Normal	Count	27	25	30	82
		%	90.0%	83.3%	100.0%	91.1%
Total		Count	30	30	30	90
%		100.0%	100.0%	100.0%	100.0%	
			Value		P	
Pearson Chi-Square			11.963[a]		.018	

Table 2: *Changes in TSH levels.*

			1m	1w	Bef	Total
FT4	High	Count	9	5	0	14
		%	30.0%	16.7%	0.0%	15.6%
	Low	Count	0	3	0	3
		%	0.0%	10.0%	0.0%	3.3%
	Normal	Count	21	22	30	73
		%	70.0%	73.3%	100.0%	81.1%
Total		Count	30	30	30	90
%		100.0%	100.0%	100.0%	100.0%	
			Value		P	
Pearson Chi-Square			16.714a		.002	

Table 3: *Changes in FT4 levels.*

			1m	1w	Bef	Total
FT3	High	Count	4	2	0	6
		%	13.3%	6.7%	0.0%	6.7%
	Low	Count	1	2	1	4
		%	3.3%	6.7%	3.3%	4.4%
	Normal	Count	25	26	29	80
		%	83.3%	86.7%	96.7%	88.9%
Total		Count	30	30	30	90
%		100.0%	100.0%	100.0%	100.0%	
			Value		P	
Pearson Chi-Square			4.825[a]		.306	

Table 4: *Changes in FT3 levels.*

decrease in hormone synthesis is transient, however, and thyroid hormone synthesis resumes in spite of continued excess iodine administration. This latter phenomenon apparently serves to defend the thyroid from iodine-induced hypothyroidism and goiter and has been termed the "adaptation or escape" from the "acute Wolff-Chaikoff effect" [11].

The aim of this work was evaluation of thyroid gland dysfunctions for patients with hepatocellular carcinoma after treatment with TACE.

Our results showed sub-clinical changes in the thyroid hormones levels in some patients after exposure to TACE, showing increasing or decreasing in their level. First the changes in TSH level after one weak we had 4 patients (13.3%) with high levels, one patients (3.3%) with low level, and 25 patients (83.3%) stay within normal. One month later the patients with high TSH level got normal levels, and one patient with low TSH level still had it low. Also 2 (8%) patients with normal TSH level at one week got low TSH level with statistically significant difference ($p < 0.05$). We found changes in FT4that after one weak 5 patients (16.7%) had high level and 3 patients (10%) had low level. After one month 9 (30%) patients had their FT4 level high, all patients with low level become normalized with statistically significant difference ($p < 0.05$). Also the changes in FT3 levels after one weak there were 2 patients (6.7%) had high FT3 level and 2 patients (6.7%) had low FT3 level. After one month there were 4 patients (13.3%) had high FT3 level and one patient had low FT3 level with no statistically significant difference ($p > 0.05$). All these changes in thyroid hormones levels were not accompanied with apparent clinical manifestations of hypo- or hyperthyroidism. They have been reported the first controlled study of ICM associated with thyrotoxicosis amongst 178 and 76 cases with incident hypothyroidism and incident overt hyperthyroidism respectively, in an iodine sufficient region [12].

Flohr., *et al*. 2008 evaluated different kinds of thyroid dysfunctions after exposure to TACE. They retrospectively analyzed a cohort of 219 patients with histologically proven HCC who were treated with TACE between 1997 and 2007. Thyroid- stimulating hormone (TSH) levels before and after TACE were available from 138 of 219 patients. TSH suppression was observed after TACE in 23 of 138 patients (16.7%). Among them, four patients developed clinical hyperthyroidism requiring medical therapy; 19 patients developed subclinical hyperthyroidism, In 19 of 138 patients (13.8%), TSH levels increased from a mean before TACE of 3.08 U/mL to a mean of 22.45 U/mL after TACE (range 4.59-76.66 U/mL). Although six patients showed a transient hypothyroidism with spontaneous normalization of TSH within 3.2 months, seven patients were lost to follow-up and six patients developed clinical hypothyroidism that required substitution therapy [13].

Another study evaluated the effect of iodinated contrast media (ICM) exposure and the risk of thyroid dysfunctions. A case control study among a broadly-representative community-based cohort of patients receiving care within Harvard Vanguard Medical Associates from 1996 to 2012. Overall, the source cohort was comprised of 349,869 qualifying patient intervals, among which 3822 incident hyperthyroid cases, 7001 incident hypothyroid, and 339,046 eligible euthyroid controls were identified. They observed that ICM exposure was associated with increased risk of incident hyperthyroidism [odds ratio, 1.61 (95% CI) 1.27-2.04], incident overt hyperthyroidism [odds ratio, 1.62 (95% CI) 1.08- 2.43], and incident overt hypothyroidism [odds ratio 2.01 (95% CI) 1.25-3.23] [14].

In two small studies, subclinical hypothyroidism developed in four of 22 German patients [15] and in three of 56 US patients [16] one week following either coronary angiography or iodinated CT. Another Japanese report of 214 women described that those with pre-existing subclinical hypothyroidism were more likely to develop overt hypothyroidism than those who were euthyroid following hysterosalpingography (35 and 2%, respectively) [17]. Iodinated contrast use can also predispose individuals to iodine-induced hyperthyroidism, particularly in those with underlying nodular thyroid disease. A German study demonstrated that serum TSH concentrations remained decreased 42 days (although still within the normal range) following iodine exposure from endoscopic retrograde cholangiopancreatography (ERCP) among 70 patients [18]. Another case report described a 62-year-old Japanese woman who developed iodine-induced thyroid storm 5h after an iodinated CT scan [19]. In a large recent case–control study spanning 20 years in the USA, a region that is con-

sidered generally iodine-sufficient, iodinated contrast media use was associated with increased incidences of hyperthyroidism and overt hypothyroidism (both occurring at a median of approximately 9 months following iodine exposure [12]**.** So our conclusion that thyroid dysfunctions after TACE could be presented by hypo or hyper-thyroidism, and patients who will be subjected to repeated TACE must have evaluations of their thyroid function.

Disclosure

We declare that we did not receive any financial support for this work.

Acknowledgments

We would like to thank Hepatoma group Ain Shams University that I have honor to be one of them for their support for this work.

Bibliography

1. Takayasu K., *et al*. "Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients". *Gastroenterology* 131 (2006): 461-469.

2. Miraglia R., *et al*. "Efficacy of transcatheter embolization /chemoembolization (TAE/TACE) for the treatment of single hepatocellular carcinoma". *World Journal of Gastroenterology* 13 (2007): 2952-2955.

3. Guerbet Laboratoires, Aulnay sous Bois, (also listed as Roissy). France, and in the United States through Savage Laboratories, Melville, NY, Wolff-MD 80 (2001): 20.

4. Katzberg RW and Haller C. "Contrast-induced nephrotoxicity: clinical landscape". *Kidney International* (2006): 3-7.

5. Moisey RS., *et al*. "Thyroiditis and iodide mumps following an angioplasty". *Nephrology Dialysis Transplantation* 22 (2007): 1250-1252.

6. Van der Molen AJ., *et al*. "Effect of iodinated contrast media on thyroid function in adults". *European Radiology* 14 (2004): 902-907.

7. Trumbo P., *et al*. "Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc". *Journal of the American Dietetic Association* 101 (2001): 294-301.

8. Bruix J and Sherman M. "AASLD practice guideline: management of hepatocellular carcinoma: An update". *Hepatology* 5 (2010): 1-35.

9. Wolff J and Chaikoff IL. "Plasma inorganic iodide as homeostatic regulation of thyroid function". *Journal of Biological Chemistry* 174 (1984): 555.

10. Braverman LE. "Changes in thyroidal function during adaptation to large doses of iodide". Proceedings of the International MERCK's Symposium, Dusseldorf (1990): 45.

11. Wolff J., *et al*. "The temporary nature of the inhibitory action of excess iodide on organic iodine synthesis in the normal thyroid". *Endocrinology* 45 (1949): 504.

12. Rhee CM., *et al*. "Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism". *Archives of Internal Medicine* 172 (2012): 153-159.

13. Flohr F., *et al*. "Hypothyroidism in patients with hepatocellular carcinoma treated by transarterial chemoembolization". *Hepatology* 47 (2008): 2144.

14. Rhee CM., *et al*. "Iodinated contrast media exposure and incident hyperthyroidism an hypothyroidism in a community based cohort". *Endocrinology Studies* 3 (2013): 27-30.

15. Gartner W and Weissel M. "Do iodine-containing contrast media induce clinically relevant changes in thyroid function parameters of euthyroid patients within the first week?" *Thyroid* 14 (2004): 521-524.

16. Koroscil TM., *et al*. "Short-term effects of coronary angiographic contrast agents on thyroid function". *Endocrine Practice* 3 (1997): 219-221.

17. Mekaru K., *et al*. "Thyroid function after hysterosalpingography using an oil-soluble iodinated contrast medium". *Gynecological Endocrinology* 24 (2008): 498-501.

18. Fassbender WJ., *et al*. "Thyroid function, thyroid immunoglobulin status, and urinary iodine excretion after enteral contrast-agent administration by endoscopic retrograde cholangio-pancreatography". *Endoscopy* 33 (2001): 245-252.

19. Shimura H., *et al*. "T4-thyroid storm after CT-scan with iodinated contrast medium". *Journal of Endocrinological Investigation* 13 (1990): 73-76.

Volume 7 Issue 3 March 2020